

Combinatorial carbohydrate chemistry

Lisa A Marcaurelle and Peter H Seeberger*

The application of combinatorial chemistry to the synthesis of carbohydrate-based compound collections has received increased attention in recent years. New strategies for the solution-phase synthesis of oligosaccharide libraries have been reported, and the use of monosaccharides as scaffolds in the generation of combinatorial libraries has been described. Novel approaches to the assembly of carbohydrate-based antibiotics, such as aminoglycoside analogs and vancomycin derivatives, have also been disclosed.

Addresses

Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139, USA

*e-mail: seeberger@mit.edu

Current Opinion in Chemical Biology 2002, 6:289–296

1367-5931/02/\$ – see front matter

© 2002 Elsevier Science Ltd. All rights reserved.

Published online 20 March 2002

Abbreviation

RGD Arg–Gly–Asp

Introduction

Combinatorial chemistry has become an important tool in modern drug development. Although carbohydrate-based compounds hold great potential as therapeutic agents, the application of combinatorial chemistry to this class of biomolecules has only recently elicited attention. The challenges associated with carbohydrate synthesis, including laborious protecting group manipulations and the need for regioselective and stereoselective glycosylation reactions, are primarily responsible for the lack of more intense efforts. The high degree of functionalization and diverse stereochemistry of carbohydrates, the very properties that render them attractive members of compound libraries, are responsible for the complications encountered by the experimentalist. In addressing and overcoming these challenges, the synthesis of a number of carbohydrate-based libraries has been achieved. This review highlights recent progress in the combinatorial synthesis of carbohydrates, including the development of new carbohydrate-based antibiotics and the use of carbohydrates as scaffolds for the synthesis of stereodiverse libraries. Recent advancements in solid-phase oligosaccharide synthesis and its application to carbohydrate libraries is also discussed.

Several excellent articles reviewing combinatorial carbohydrate synthesis have appeared prior to 2000 [1*,2,3]. This article focuses primarily on strategies reported in the past two years. The synthesis of glycopeptide libraries and related glycoconjugates has been reviewed recently and thus will not be covered [4**,5].

Combinatorial oligosaccharide libraries

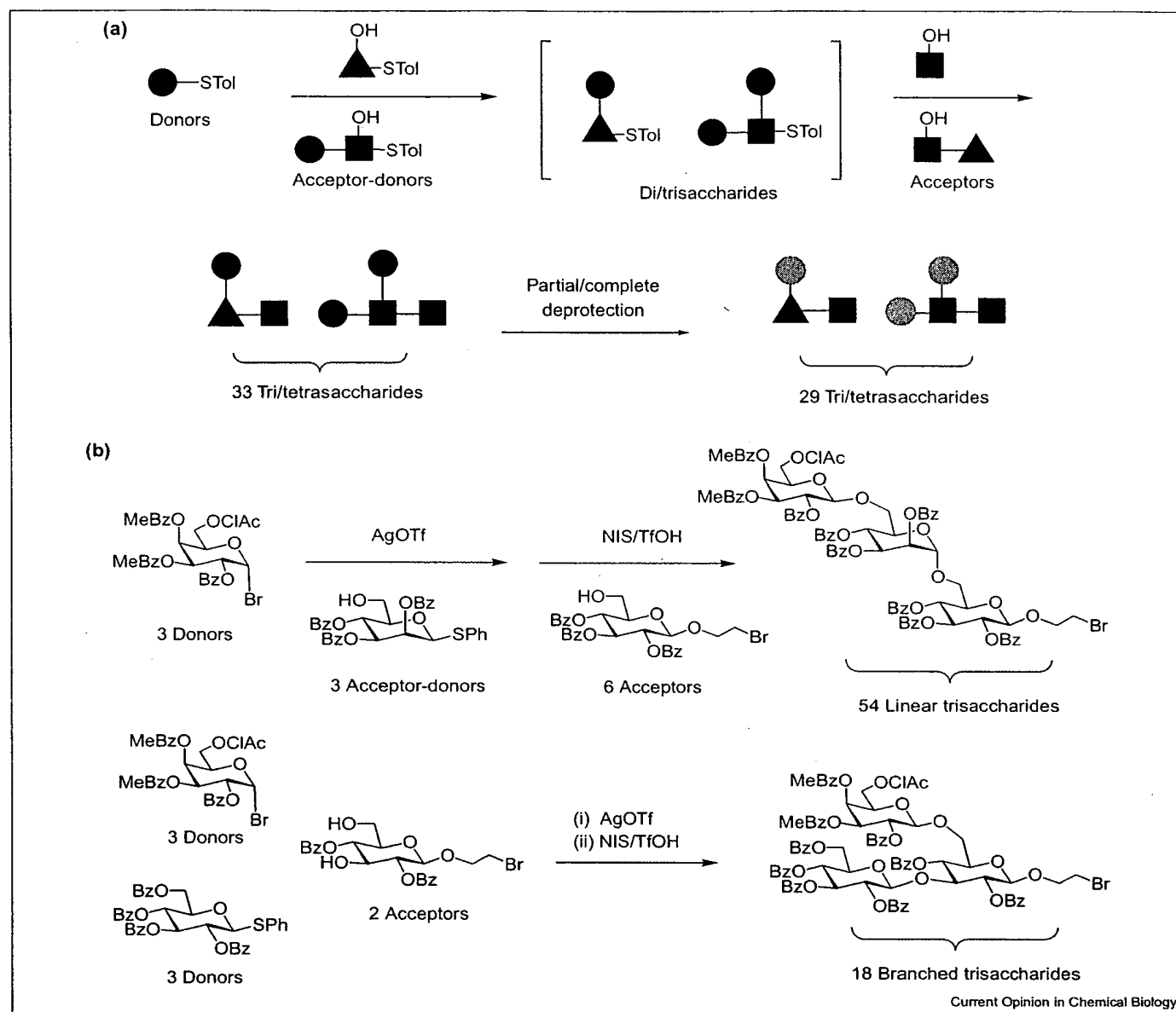
In the past five years, the combinatorial synthesis of oligosaccharide libraries has been carried out both in

solution and on solid support [1*,2,3]. During the period covered by this review, only two approaches to the combinatorial synthesis of oligosaccharides have been reported [6**,7*]. Both reports describe similar solution-phase approaches, employing sequential one-pot glycosylation strategies. Ye and Wong [6**] made use of their programmable one-pot glycosylation technology [8], which has been employed for the synthesis of a number of structures, including the tumor-associated hexasaccharide Globo-H [9*]. With the aid of anomeric reactivity values determined with the computer program OptiMer™, the construction of a small library of trisaccharides and tetrasaccharides was accomplished using a panel of monosaccharide and disaccharide donors. The sequential reaction of thioglycosides of varying reactivity produced a library of 33 oligosaccharides, which were partially or completely deprotected to create 29 additional compounds (Figure 1a).

In the second approach, Takahashi *et al.* [7*] reported the rapid assembly of a library of linear and branched trisaccharides by using a combination of donors, including glycosyl bromides, thioglycosides and 2-bromoethyl glycosides (Figure 1b). Selective activation of the bromide and thioglycoside donors with AgOTf and NIS/TfOH, respectively, enabled the generation of a library of 72 trisaccharides by sequential one-pot reactions on a manual synthesizer. It should be noted that each member of the library contains two sites for further elaboration. The chloroacetate group can be selectively removed for attachment of the trisaccharide to solid-support, while the bromoethyl glycoside can be modified by alkylation for the introduction of diversity at the anomeric position.

The synthesis of oligosaccharide libraries in solution has been quite fruitful. Still, the use of solid-phase methods for the construction of glycosidic linkages is attractive, because an excess of reagents may be used to ensure high yields and the number of purification steps is reduced. The solid-phase synthesis of oligosaccharide libraries was first reported by Kahne and co-workers [10] and later by Zhu and Boons [11]. Although no new methods for the solid-phase synthesis of oligosaccharide libraries have been reported during the past two years, a number of strategies for the solid-phase synthesis of oligosaccharides in general have been reported [12–14,15**,16*], including the automation of oligosaccharide assembly. The first automated solid-phase oligosaccharide synthesizer [15**] was used to prepare structures as large as branched dodecamers in less than one day. The synthesis was achieved using a re-engineered peptide synthesizer containing a coolable reaction vessel, utilizing glycosyl phosphates and glycosyl trichloroacetimidate building blocks (Figure 2). Each cycle involved the coupling of a building block to a growing resin-bound oligosaccharide and the removal of a protecting group to expose a single hydroxyl

Figure 1



Novel approaches to oligosaccharide libraries. (a) Wong's approach to the one-pot assembly of a library of linear and branched trisaccharides and tetrasaccharides. The sequential reaction of thioglycoside donors of varying reactivity produced a library of 33 oligosaccharides, which were partially or completely deprotected to afford 29 more compounds.

(b) Takahashi's one-pot sequential assembly of a library of trisaccharides. Selective activation of glycosyl bromide and thioglycoside donors with AgOTf and NIS/TfOH, respectively, yielded a library of 72 linear and branched trisaccharides. Bz, benzoyl group; NIS, *N*-iodosuccinimide; TfOH, trifluoromethanesulfonic acid.

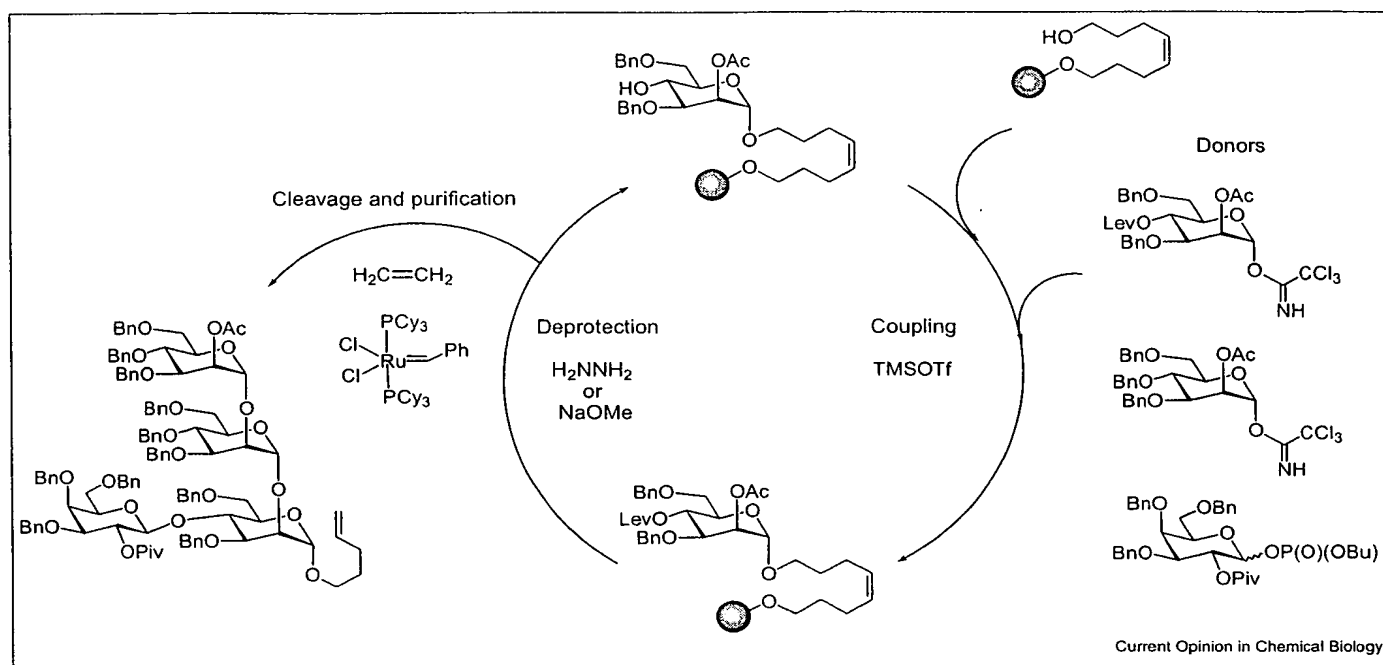
group for attachment of the next carbohydrate. A meta-thesis-cleavable octenediol linker enabled release of the oligosaccharide from the support using Grubb's catalyst. This method has recently been applied to the synthesis of a branched tetrasaccharide (Figure 2) corresponding to a portion of the cell-surface lipophosphoglycan of *Leishmania* parasites [16^{*}]. Branching of the tetrasaccharide was achieved through the selective removal of different ester protecting groups. The automation of oligosaccharide synthesis

is expected to greatly facilitate preparation of oligosaccharide libraries by parallel synthesis.

Carbohydrate scaffolds for combinatorial synthesis

Monosaccharides are particularly attractive scaffolds for the synthesis of combinatorial libraries. They are readily available, conformationally rigid, chiral and highly functionalized molecules, containing up to five hydroxyl

Figure 2



Solid-phase synthesis of a branched tetrasaccharide [16*] using an automated oligosaccharide synthesizer [15**]. Bn, benzyl group. Cy, cyclohexyl group; Lev, levulinoyl group; Piv, pivaloyl group.

groups for the introduction of a diverse range of side chains. A variety of synthetic routes to these scaffolds have been reported [17,18] since carbohydrates were first described as ‘privileged platforms’ [19,20].

Recently, a focused combinatorial library of 126 mimetics of the Arg–Gly–Asp (RGD) peptidic sequence based on a sugar scaffold was rationally designed aided by molecular modeling [21*]. Although carbohydrate scaffolds had previously served as peptidomimetics, this was the first report of a combinatorial library of this class of compounds. D-Xylose was selected as a scaffold for the introduction of acidic and basic functional groups at various positions in order to achieve a high degree of stereodiversity. The α - and β -allyl glycosides of D-xylose (Figure 3a) were modified by benzylation to yield a total of 14 compounds, composed of a mixture of mono-, di- and trihydroxy derivatives. Alkylation with *t*-butylbromoacetate fashioned the corresponding ester derivatives. Using a ‘mix-and-split strategy’, the 14 compounds were elaborated into a library of 126 members that were functionalized with various amines. Using this strategy, an RGD mimic was identified that displayed activity equal to a known peptide-based inhibitor (RGDS) of integrin-mediated adhesion. The active compound contained an α -linked *N*-propyl substituent and a carboxylic acid at position 4. This method is now being applied to the synthesis of libraries of other biologically relevant peptidomimetics.

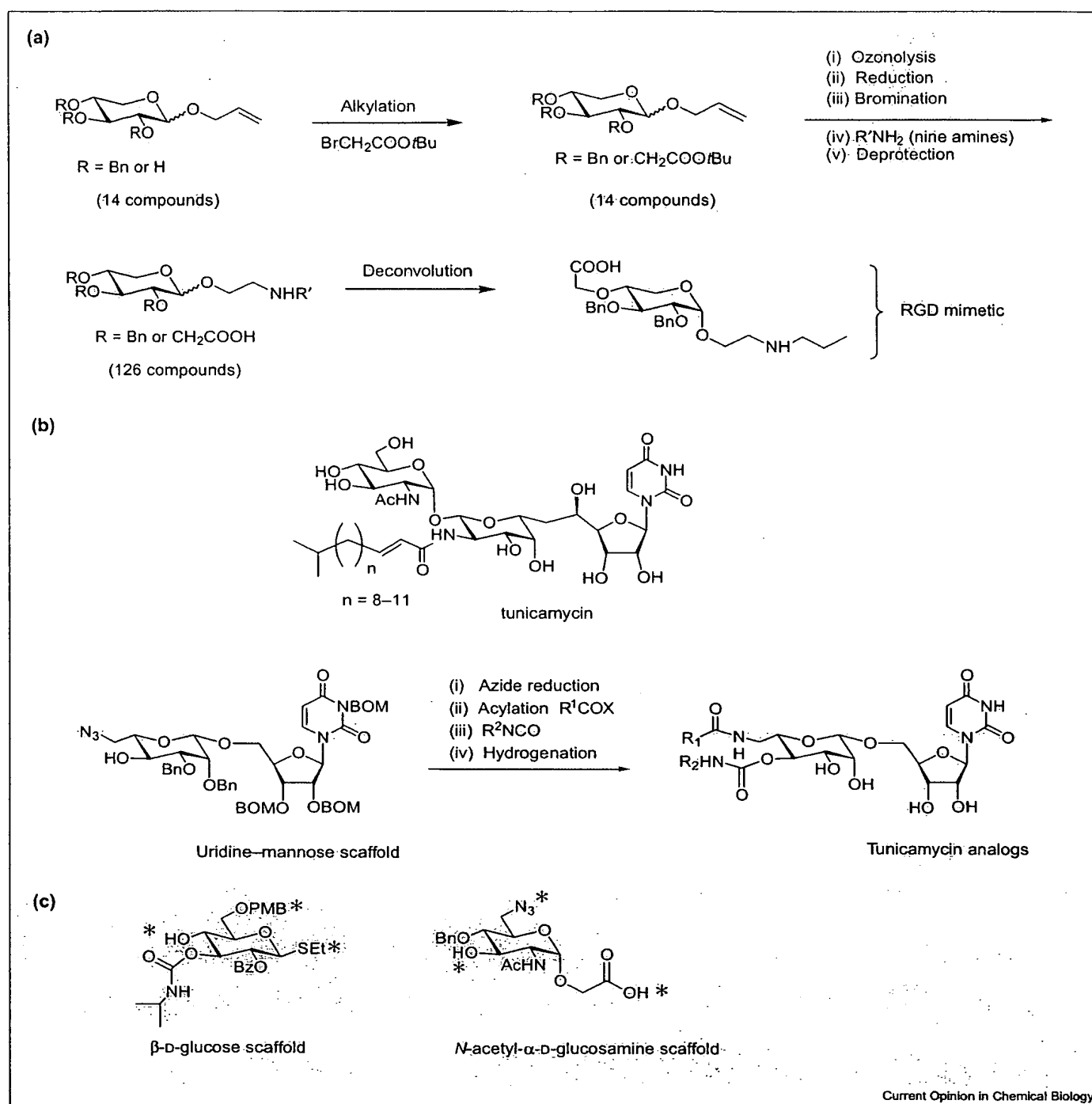
A second recently reported carbohydrate scaffold is based on tunicamycin (Figure 3b; [22]). Tunicamycins have been shown to inhibit a wide variety of lipid carrier-dependent protein glycosylations and are potential antibiotics, as they inhibit bacterial cell wall biosynthesis. Tunicamycins have not been used as therapeutics because they are toxic to mammalian cells, inhibiting all *N*-linked glycosylation. Analogs of tunicamycin may exhibit specific inhibitory effects towards eukaryotic and prokaryotic cells, potentially allowing for the targeting of pathogenic cells over mammalian cells. The tunicamycin scaffold incorporates two sites that can be derivatized orthogonally, an azide and a hydroxyl group (Figure 3b). Following azide reduction, modification of the disaccharide scaffold by acylation and amidation may generate a library of tunicamycin analogs.

Two additional scaffolds have been reported during the past two years (Figure 3c). The β -D-glucose [23] and *N*-acetyl- α -D-glucosamine [24] derived structures were synthesized for the purpose of generating carbohydrate-based libraries for broad screening and can be decorated at the positions indicated by asterisks in Figure 3c. The glucose scaffold is amenable to solid-support synthesis, resulting in an immobilized thioglycoside donor. Further diversity could be generated at the anomeric position by glycosylation.

Libraries of carbohydrate-based antibiotics

A number of antibiotics contain a glycan portion [25**]. Examples of carbohydrate-based antibiotics include

Figure 3



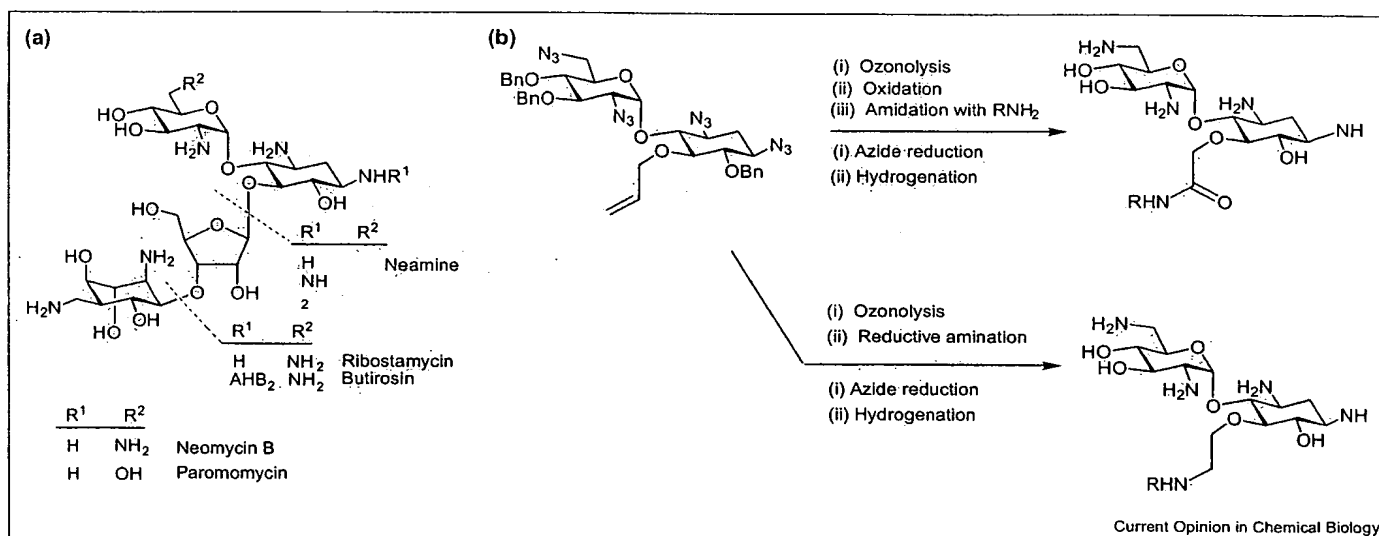
Use of carbohydrates as scaffolds for combinatorial synthesis. (a) Synthesis of a combinatorial library of peptidomimetics of the RGD sequence using D-xylose as a sugar scaffold [21]. An RGD-mimic that was identified from the library is shown. (b) Structure of Sofia's carbohydrate scaffold based on

tunicamycin containing two sites for functionalization. [22]. (c) Structure of carbohydrate scaffolds derived from β -D-glucose [23] and N-acetyl- α -D-glucosamine [24]. Sites for functionalization are indicated (*). BOM, benzyloxy methyl; PMB, *para*-methoxybenzyl group.

aminoglycosides, such as neomycin, kanamycin and streptomycin, and the glycopeptides vancomycin and teicoplanin. Because of the recent emergence of a number

of drug-resistant bacterial strains, much effort has been focused on the generation of new structures with improved antibiotic activity. Wong and co-workers [26–28] have

Figure 4



Synthesis of aminoglycoside libraries based on neamine assembled by reductive amination and amidation [29].

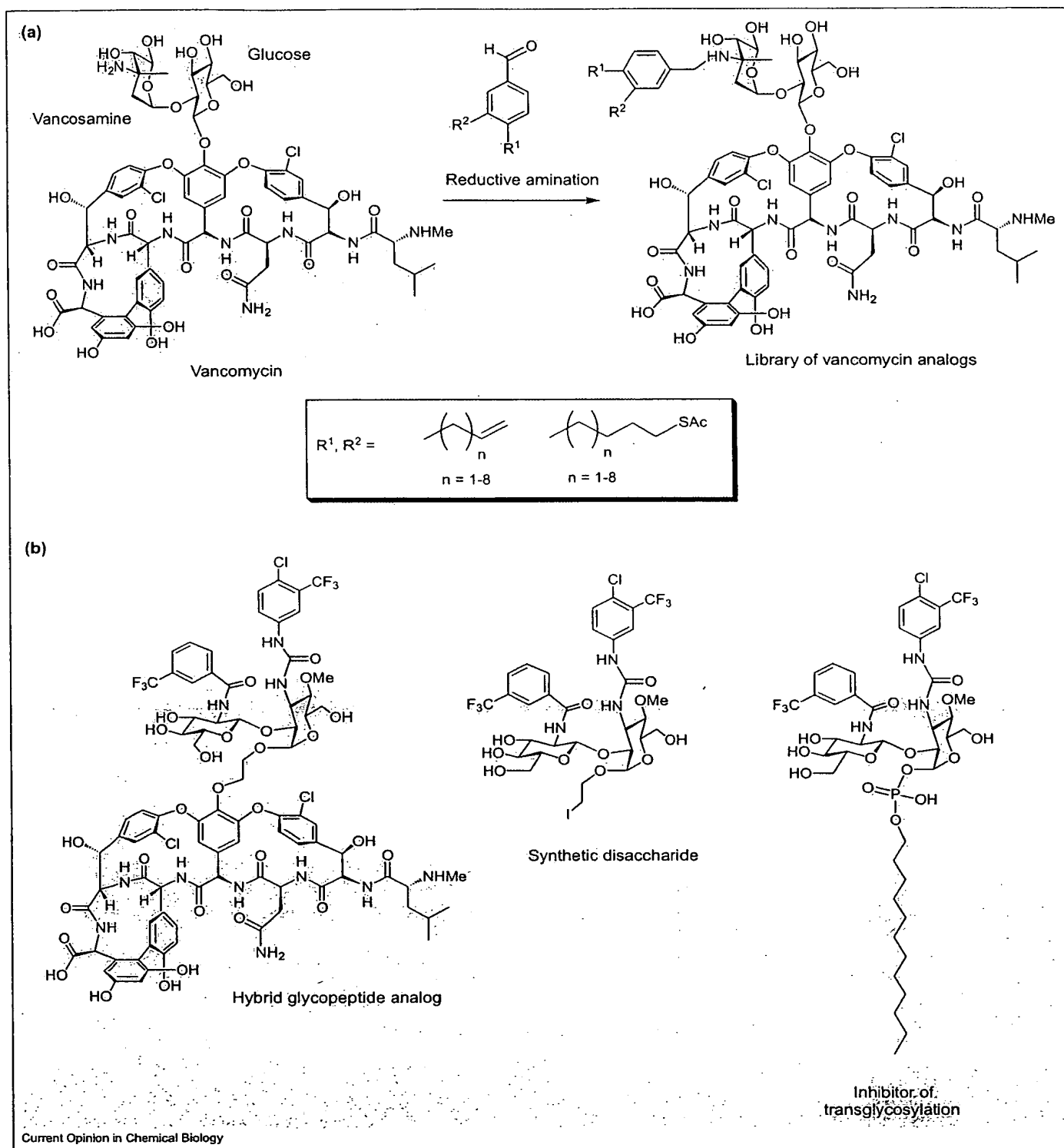
reported a number of library-based approaches for the discovery of new aminoglycoside antibiotics. Because of the size and complexity of aminoglycosides such as neomycin (Figure 4), a primary focus for the design of new antibiotics is the identification of simpler structures that retain the activity of the parent compound. Over the course of their studies, Wong *et al.* identified the naturally occurring pseudodisaccharide neamine as a core structure for the generation of new libraries of aminoglycoside mimetics [28]. A recent report described the synthesis of a library of neamine-based compounds and their RNA-binding properties [29]. The neamine library was constructed by reaction of the corresponding azide precursor with a variety of amines after conversion of the 5-*O*-allyl group to a reactive chemical handle (Figure 4). Amidation or reductive amination of the intermediate acid or aldehyde, followed by azide reduction and hydrogenation, yielded a library of compounds modified at the C-5 position of neamine.

The glycopeptide vancomycin (Figure 5a) has been used clinically for the past 40 years to treat infection by Gram-positive bacteria. The emergence of resistance to vancomycin in enterococcal strains has aroused considerable concern [30] and spurred vigorous efforts to develop novel antibiotics to combat these strains. In a series of recent reports, Nicolaou and co-workers [31,32,33**] described the construction of several libraries of vancomycin analogs, modified within the carbohydrate portion of the glycopeptide. Initial efforts were directed towards the replacement of the naturally occurring disaccharide with a panel of synthetic monosaccharides [31]. The glycosylation was performed on solid-phase using trichloroacetimidate donors, with the aglycone attached to the resin by a new selenium-based safety-catch linker [32]. The monosaccharide

analogs proved to be less active than the parent vancomycin against all bacterial strains. Having established the importance of the vancosamine moiety for antibacterial activity Nicolaou and co-workers turned their attention to the modification of the existing glycan by reductive amination. Reaction of vancomycin with a variety of substituted benzaldehydes (containing terminal alkenes or thioacetates) yielded a library of vancomycin analogs (Figure 5a). Biological evaluation of this library revealed several highly potent compounds effective against vancomycin-resistant strains. Dimerization of these compounds by disulfide formation and olefin metathesis led to the identification of an additional set of highly potent antibiotics [33**]. In this case, the discovery of active compounds was facilitated through the use of target-accelerated combinatorial synthesis (or dynamic combinatorial synthesis) [34,35].

It has been suggested that glycolipid derivatives of vancomycin (i.e. compounds containing a lipid-functionalized disaccharide) are active against resistant strains of bacteria because of their ability to inhibit the transglycosylation step of peptidoglycan biosynthesis [36,37]. If this model is correct, it should be possible to improve the activity of vancomycin derivatives by optimizing the glycolipid moiety for inhibition of transglycosylation. In order to test this hypothesis, Kahne and co-workers [38] devised a strategy for the synthesis of a new class of vancomycin analogs, termed hybrid glycopeptide antibiotics. To illustrate their approach, the aglycone was modified by alkylation with a synthetic disaccharide, corresponding to an analog of the known transglycosylase inhibitor moenomycin (Figure 5b). This disaccharide had been identified from a combinatorial library of moenomycin analogs [39]. The resulting hybrid

Figure 5



Strategies for the synthesis of vancomycin analogs. (a) Nicolaou's synthesis of vancomycin analogs by reductive amination with benzaldehyde derivatives, containing terminal alkenes and thioacetates [31]. Dimerization of the vancomycin analogs (by disulfide formation or

olefin metathesis) led to the identification of potent antibiotics with activity against resistant bacterial strains [33**]. (b) Kahne's hybrid glycopeptide antibiotic, containing a disaccharide analog of the transglycosylase inhibitor moenomycin [38].

molecule, which contains the vancomycin aglycone in place of the lipid moiety, exhibits antibiotic activity far exceeding that of the individual components. This approach should greatly facilitate the synthesis of a large collection of vancomycin analogs, because the synthetically challenging glycosidic linkage is replaced with a simple ethylene glycol linker.

Conclusions

In light of the biological importance of oligosaccharides [40], the development of new strategies for their preparation is key to the advancement of our understanding of various carbohydrate-protein interactions and the discovery of new therapeutic agents. The application of combinatorial synthesis to the production of carbohydrate-based libraries has received increased attention in recent years. Combinatorial strategies have been applied to the discovery of new carbohydrate-based antibiotics, including derivatives of vancomycin [31,33,38] and aminoglycosides [29], and novel one-pot glycosylation strategies have been employed for the generation of oligosaccharide libraries [6,7]. Recent advances in solid-phase oligosaccharide synthesis, resulting in the development of an automated synthesizer [15], are expected to facilitate future progress in the assembly of carbohydrate-based libraries.

Acknowledgements

LAM would like to thank the NIH for a post-doctoral fellowship.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Schweizer F, Hinds G O: **Combinatorial synthesis of carbohydrates.** *Curr Opin Chem Biol* 1999, 3:291-298.
This is a good review of the literature prior to 1999 on the combinatorial synthesis of carbohydrates, including the preparation of libraries of oligosaccharides and glycomimetics, and the use of carbohydrates as scaffolds.
2. Sofia MJ: **Carbohydrate-based combinatorial libraries.** *Mol Diversity* 1998, 3:75-94.
3. Kahne D: **Combinatorial approaches to carbohydrates.** *Curr Opin Chem Biol* 1997, 1:130-135.
4. St Hilaire PM, Meldal M: **Glycopeptide and oligosaccharide libraries.** *Angew Chem Int Ed Engl* 2000, 39:1162-1179.
This is an excellent review on the synthesis of glycopeptide and oligosaccharide libraries, including the screening of carbohydrate-protein interactions.
5. Barkley A, Arya P: **Combinatorial chemistry toward understanding the function(s) of carbohydrates and carbohydrate conjugates.** *Chemistry* 2001, 7:555-563.
6. Ye X-S, Wong C-H: **Anomeric reactivity-based on one-pot oligosaccharide synthesis: a rapid route to oligosaccharide libraries.** *J Org Chem* 2000, 65:2410-2431.
The OptiMer™ strategy was applied to the rapid assembly of a library of trisaccharides and tetrasaccharides. This was one of the first oligosaccharide libraries created by a one-pot approach.
7. Takahashi T, Adachi M, Matsuda A, Doi T: **Combinatorial synthesis of trisaccharides via solution-phase one-pot glycosylation.** *Tetrahedron Lett* 2000, 41:2599-2603.
A library of 72 trisaccharides was constructed from a set of different glycosyl donors and selective activators. The solution-phase assembly of the library was achieved using a manual synthesizer.
8. Zhang Z, Ollman IR, Ye X-S, Wischnat R, Baasov T, Wong C-H: **Programmable one-pot oligosaccharide synthesis.** *J Am Chem Soc* 1999, 121:734-755.
9. Burkhart F, Zhang ZY, Wacowich-Sgarbi S, Wong CH: **Synthesis of the Globo-H hexasaccharide using the programmable reactivity-based one-pot strategy.** *Angew Chem Int Ed Engl* 2001, 40:1274-1277.
The potential of the OptiMer™ strategy for synthesis planning was demonstrated with the one-pot synthesis of the tumor-associated carbohydrate antigen Globo-H.
10. Liang R, Yan L, Loebach J, Ge M, Uozumi Y, Sekanina K, Horan N, Gildersleeve J, Thompson C, Smith AB *et al.*: **Parallel synthesis and screening of a solid phase carbohydrate library.** *Science* 1996, 274:1520-1522.
11. Zhu T, Boons G-J: **A two-directional approach for the solid-phase synthesis of trisaccharide libraries.** *Angew Chem Int Ed Engl* 1998, 37:1898-1900.
12. Zhu T, Boons G-J: **A novel and efficient synthesis of a dimeric Le(x) oligosaccharide on polymeric support.** *J Am Chem Soc* 2000, 122:10222-10223.
13. Knerr L, Schmidt R: **Solid-phase synthesis of a branched hexasaccharide related to the lacto-N-hexaose.** *Eur J Org Chem* 2000:2803-2808.
14. Roussel F, Knerr L, Schmidt R: **Solid-phase synthesis of lactose-containing oligosaccharides.** *Eur J Org Chem* 2001:2067-2073.
15. Plante OJ, Palmacci ER, Seeberger PH: **Automated solid-phase synthesis of oligosaccharides.** *Science* 2001, 291:1523-1527.
The authors describe the first automated solid-phase oligosaccharide synthesizer for the assembly of linear and branched structures up to dodecasaccharides. This synthesizer may eventually facilitate the rapid parallel preparation of oligosaccharide libraries.
16. Hewitt MC, Seeberger PH: **Automated solid-phase synthesis of a branched Leishmania cap tetrasaccharide.** *Org Lett* 2001, 3:3699-3702.
This automated synthesis of a branched tetrasaccharide was carried out on the solid-phase oligosaccharide synthesizer. Branching of the oligosaccharide was achieved through the selective removal of different ester-protecting groups.
17. Wunberg T, Kallus C, Opatz T, Henke S, Schmidt W, Kunz H: **Carbohydrates as multifunctional chiral scaffolds in combinatorial synthesis.** *Angew Chem Int Ed Engl* 1998, 37:2503-2505.
18. Sofia MJ, Hunter R, Chan TY, Vaughan A, Dulina R, Wang H, Gange D: **Carbohydrate-based small-molecule scaffolds for the construction of universal pharmacophore mapping libraries.** *J Org Chem* 1998, 63:2802-2803.
19. Hirschmann R, Nicolaou KC, Pietranico S, Leahy EM, Salvino J, Arison B, Cichy MA, Spoors PG, Shakespeare WC, Sprengeler PA *et al.*: **De novo design and synthesis of somatostatin non-peptide peptidomimetics utilizing β-D-glucose as a novel scaffolding.** *J Am Chem Soc* 1993, 115:12550-12568.
20. Hirschmann R, Hynes JJ, Cichy-Knight MA, van Rijn RD, Sprengeler PA, Spoors PG, Shakespeare WC, Pietranico-Cole S, Barbosa J, Liu J *et al.*: **Modulation of receptor and receptor subtype affinities using diastereomeric and enantiomeric monosaccharide scaffolds as a means to structural and biological diversity. A new route to ether synthesis.** *J Med Chem* 1998, 41:1382-1391.
21. Moitessier N, Dufour S, Chretien F, Thiery JP, Maigret B, Chapleur Y: **Design, synthesis and preliminary biological evaluation of a focused combinatorial library of stereodiverse carbohydrate-scaffold-based peptidomimetics.** *Bioorg Med Chem* 2001, 9:511-523.
This was the first report of a library of peptidomimetics constructed from a carbohydrate scaffold.
22. Silva DJ, Sofia MJ: **Novel carbohydrate scaffolds. Assembly of a uridine-mannose scaffold based on tunicamycin.** *Tetrahedron Lett* 2000, 41:855-858.
23. Hirschmann R, Ducry L, Smith AB III: **Development of an efficient, regio- and stereoselective route to libraries based on the beta-D-glucose scaffold.** *J Org Chem* 2000, 65:8307-8316.
24. Ghosh M, Dulina RG, Kakarta R, Sofia MJ: **Efficient synthesis of a stereochemically defined carbohydrate scaffold: carboxymethyl 2-acetamido-6-azido-4-O-benzyl-2-deoxy-alpha-D-glucopyranoside.** *J Org Chem* 2000, 65:8387-8390.

25. Ritter TK, Wong CH: Carbohydrate-based antibiotics: a new approach to tackling the problem of resistance. *Angew Chem Int Ed Engl* 2001, 40:3508-3533.
- This is an excellent review on the identification of new targets and strategies for antibiotic discovery, including the development of small-molecules as antibiotics to target carbohydrate receptors or carbohydrate-modifying enzymes. The use of modified aminoglycosides and glycopeptides as new antibiotics is discussed.
26. Park WKC, Auer M, Jaksche H, Wong CH: Rapid combinatorial synthesis of aminoglycoside antibiotic mimetics: use of a polyethylene glycol-linked amine and a neamine-derived aldehyde in multiple component condensation as a strategy for the discovery of new inhibitors of the HIV RNA Rev responsive element. *J Am Chem Soc* 1996, 118:10150-10155.
27. Wong CH, Hendrix M, Manning DM, Rosenbohm C, Greenberg WA: A library approach to the discovery of small molecules that recognize RNA: use of a 1,3-hydroxyamine motif as core. *J Am Chem Soc* 1998, 120:8319-8327.
28. Greenberg WA, Priestly ES, Sears PS, Alper PB, Rosenbohm C, Hendrix M, Hung S-C, Wong CH: Design and synthesis of new aminoglycoside antibiotics containing neamine as an optimal core structure: correlation of antibiotic activity with *in vitro* inhibition of translation. *J Am Chem Soc* 1999, 121:6527-6541.
29. Sucheck SJ, Greenberg WA, Tolbert TJ, Wong CH: Design of small molecules that recognize RNA: development of aminoglycosides as potential antitumor agents that target oncogenic RNA sequences. *Angew Chem Int Ed Engl* 2000, 39:1080-1083.
30. Walsh C: Molecular mechanisms that confer antibacterial drug resistance. *Nature* 2000, 406:775-781.
31. Nicolaou KC, Cho SY, Hughes R, Winssinger N, Smethurst C, Labischinski H, Endermann R: Solid- and solution-phase synthesis of vancomycin and vancomycin analogues with activity against vancomycin-resistant bacteria. *Chemistry* 2001, 7:3798-3823.
32. Nicolaou KC, Winssinger N, Hughes R, Smethurst C, Cho SY: New selenium-based safety catch linkers: solid-phase semisynthesis of vancomycin. *Angew Chem Int Ed Engl* 2000, 39:1084-1088.
33. Nicolaou KC, Hughes R, Cho SY, Winssinger N, Labischinski H, Endermann R: Synthesis and biological evaluation of vancomycin dimers with potent activity against vancomycin-resistant bacteria: target accelerated combinatorial synthesis. *Chemistry* 2001, 7:3824-3843.
- The dimerization of vancomycin analogs was achieved by disulfide formation and olefin metathesis to give a number of highly potent antibiotics with activity against vancomycin-resistant bacterial strains. Combinatorial synthesis of the dimer libraries was carried out in the presence of vancomycin's target $\text{Ac}_2\text{-L-Lys-D-Ala-D-Ala}$.
34. Ganesan A: Strategies for the dynamic integration of combinatorial synthesis and screening. *Angew Chem Int Ed Engl* 1998, 37:2828-2831.
35. Lehn J-M: Dynamic combinatorial chemistry and virtual combinatorial libraries. *Chemistry* 1999, 5:2455-2463.
36. Ge M, Chen Z, Onishi HR, Kohler J, Silver LL, Kerns R, Fukuzawa S, Thompson C, Kahne D: Vancomycin derivatives that inhibit peptidoglycan biosynthesis without binding D-Ala-D-Ala. *Science* 1999, 284:507-511.
37. Kerns R, Dong SD, Fukuzawa S, Carbeck J, Kohler J, Silver LL, Kahne D: The role of hydrophobic substituents in the biological activity of glycopeptide antibiotics. *J Am Chem Soc* 2000, 122:12608-12609.
38. Sun B, Chen Z, Eggert US, Shaw SJ, LaTour JV, Kahne D: Hybrid glycopeptide antibiotics. *J Am Chem Soc* 2001, 123:12722-12723.
39. Sofia MJ, Allanson N, Hatzenbuehler NT, Jain R, Kakarla R, Kogan N, Liang R, Liu D, Silva DJ, Wang H *et al.*: Discovery of novel disaccharide antibacterial agents using a combinatorial library approach. *J Med Chem* 1999, 42:3193-3198.
40. Varki A: Biological roles of oligosaccharides: all of the theories are correct. *Glycobiology* 1993, 3:97-130.